Structural basis for modulation and agonist specificity of HCN pacemaker channels

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The family of hyperpolarization-activated, cyclic nucleotidemodulated (HCN) channels are crucial for electrical signaling in the heart. These nonselective cation channels are activated by membrane hyperpolarization and modulated by the binding of cyclic nucleotides, such as cAMP. The cAMP mediated enhancement of channel activity is largely responsible for the increase in heart rate caused by b-adrenergic agonists. This work used x-ray diffraction to determine the structure of a HCN fragment. The results yielded important insight into the way the structure modulates the channel and provides specificity to the agonist. This work has important implications for heart therapies.

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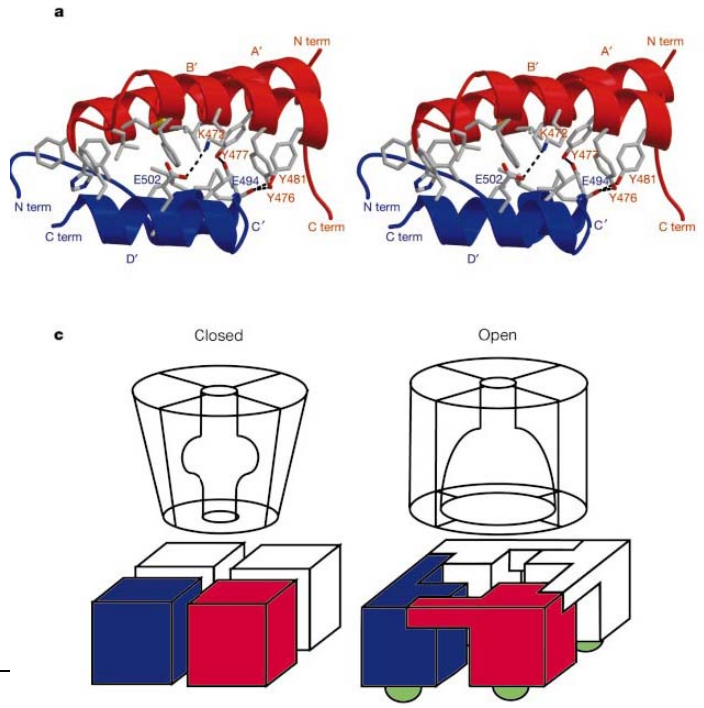

Cartoon of the C-linker interactions and cyclic nucleotide-dependent tetramer formation in an unliganded closed channel (left) and a liganded open channel (right).